REMARKS

This is in response to the United States Patent and Trademark Office communication dated May 20, 2004, to comply the claims in the response to the United States Patent and Trademark Office Action filed May 13, 2004. No new matter has been added. The following Remarks are as previously presented.

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-64 are in this case. Claims 63 and 64 were withdrawn under a restriction requirement as drawn to a non-elected invention. Claims 1-62 have been rejected. Claims 1-36, 39 and 41 have now been canceled. New Claims 65-72 have now been added.

Drawings

A Petition To Accept Color Drawings is enclosed together with three sets of formal color drawings.

35 U.S.C. § 103(a) Rejections - U.S. Patent No. 5,822,447 to Kasdan

The Examiner has rejected Claims 1-13, 15-29, 31-38 and 40-53 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,822,447 to Kasdan. The Examiner's rejections are respectfully traversed. Claims 1-13, 15-29, 31-36 and 41 have now been canceled, rendering moot the Examiner's rejection of these claims. Claims 37-38, 40, 42-45 and 48-51 have now been amended and new Claims 65-70 have now been added.

The Examiner contends that Applicant has admitted prior art in view of which Claims 1-13, 15-29, 31-38 and 40-53 are unpatentable over Kasdan. Specifically, the Examiner rejects method claims 37-38, 45-46 and 48-52 based upon the contention that Kasdan discloses a method for generating a profile of particulate components of a body fluid sample comprising: (a) a device for causing controlled flow of the body fluid sample leading to a differential distribution of the particulate components on a substrate (column 1, lines 24-26), said controlled flow of the body fluid sample leading to a differential distribution of the particulate components on said substrate; and (b) a magnifying device being for providing a magnified image of differentially

distributed particulate components on said substrate (column 2, lines 58-66), said magnified image representing a profile of said particulate components of the body fluid sample (column 2, lines 30-34). The Examiner concedes that Kasdan is silent about controlled flow of the body fluid sample leading to a differential distribution of the particulate components on said substrate, but nevertheless contends that Applicant's background invention discloses this feature as well known in the art. The Examiner concludes that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to provide the feature as though by Applicant's prior art about controlled flow of the body fluid sample leading to a differential distribution of the particulate components on said substrate with the method of Kasdan in order to improve the assessment of a patient's overall health (making reference to specification, background section, pages 1-2).

The Examiner further contends that Kasdan discloses an imaging device being for capturing said magnified image provided by said magnifying device (Fig. 1) which is a camera (column 2, lines 58-57).

Applicant vigorously disagrees with the Examiner's contention that the Applicant has provided prior art in view of which Claims 1-13, 15-29, 31-38 and 40-53 are unpatentable over Kasdan.

In the first place, Applicant wishes to respectfully point out that, in very sharp contrast to the Examiner's contention, pages 1-2 of the specification clearly do not refer to any prior art whatsoever relating in general to "*controlled flow of a body fluid sample leading to a differential distribution of the particulate components on said substrate*", which is cited by the Examiner, and which relates to a central non-obvious aspect of the present invention. This is in accordance with the Examiner's failure to cite any specific relevant prior art in support of these rejections. These cited pages of the specification furthermore clearly do not refer, either explicitly or using equivalent terminology, to any prior art whatsoever relating specifically to any technical feature relating to the instant invention, including "*controlled flow*" of a body fluid, a "*body fluid sample*", "*differential distribution*" of particulate components of a body fluid, and/or a "*substrate*" underlying particulate components of a body fluid, as specifically cited by the Examiner. As such, the Examiner's contention that "*controlled flow of the body fluid sample leading to a differential distribution of the particulate components on said substrate*" is disclosed by "*Applicant's background invention*" is,

in Applicant's firm opinion, incorrect, again in accordance with the Examiner's failure to cite any specific relevant prior art in support of these rejections. As such, Applicant is of the very strong opinion that these arguments alone are sufficient to demonstrate that the Examiner's rejections are clearly unfounded and that the instant invention is clearly not rendered obvious by Kasdan in view of any prior art admitted by the specification.

Applicant wishes to further respectfully point out that prior art methods cited other than at pages 1 and 2 of the specification cited by the Examiner are methods involving "automated counters", "nephelometers", and "ELISA readers" which "are capable of counting and classifying different components of the body fluid sample on the basis of predefined characteristics... such as size, shape and concentration" (page 3, paragraph starting at line 5). In critically sharp contrast to the teachings of the instant claims, however, none of these methods suggests, employs, nor is based on achieving, and/or analyzing, differential distribution of body fluid particles on a substrate resulting from controlled flow of the body fluid, which is a complex phenomenon only indirectly/partially dependent on shape, size and/or concentration of the particles, and which is clearly a non-obvious feature of the instant claims over the prior art. Therefore since, as conceded by the Examiner that "*Kasdan is silent about controlled flow of the body fluid sample leading to a differential distribution of the particulate components on said substrate*", and since the instant specification clearly does not admit any prior art teaching same, in sharp contrast to the Examiner's contention that it does, Applicant is of the very strong opinion that the Examiner's rejections are unfounded and that the present invention is clearly not rendered obvious by Kasdan in view of prior art disclosed in Applicant's background invention.

Applicant wishes to yet further respectfully point out that in sharp contrast to the Examiner's contention that it contributes to rendering the instant claims obvious in view of prior art admitted by Applicant's background invention, Kasdan instead clearly teaches away from the instant claims. Namely, Kasdan teaches "*smearing*" of particles from a fluid sample such as a body fluid to a substrate such that the particles "*substantially do not overlap one another*" (Kasdan, column 1, sentence starting at line 64). Furthermore, Kasdan explicitly states as a general guideline for all embodiments of the invention taught therein: "*So long as the particles of interest do not overlap each other, the method of the present invention may be practiced.*"

(Kasdan, column 2, sentence starting at line 6). In critical contrast, however, achieving substantial overlapping of body fluid particles is set forth by the instant specification as an essential feature of various embodiments of the instant teachings (in general refer to the specification, page 59 line 11 to page 62, line 9; and specifically to Figures 20a-b, 21c, and 22b and legends thereof at page 20). As such, Applicant is of the very strong opinion that Kasdan clearly teaches away from the instantly claimed invention, and hence that these rejections are clearly unfounded.

Notwithstanding from the above and in the interest of expediting prosecution of this case, Applicant currently elects to amend independent claims 37 and 48 to be drawn to methods of determining presence or absence of a clinical condition, and to include the added limitation of comprising the step of comparing the profile of particulate components of an individual with that of a control body fluid sample obtained under said controlled flow to thereby determine the presence or absence of the clinical condition in the individual. According to the instant teachings, the profile of the control body fluid sample is obtained by applying the instant teachings to an actual sample so as to generate the profile, or, alternately, is obtained in the form of pre-existing data (specification, page 40, paragraph starting at line 4; page 50, sentence starting at line 13). In any case, a control profile or data derived therefrom is obtained from a sample which is subjected to the same flow conditions as the tested sample, since as is clearly described in the instant specification, flow under controlled conditions which can be duplicated is necessary in order to determine the clinical condition of the tested sample. In addition, Applicant further currently elects to add new Claims 66 and 67 depending from Claim 37, respectively limiting the individual from which the control body fluid sample is obtained to one which is healthy or one which has the clinical condition, and to add new Claims 69 and 70 depending from Claim 48, respectively limiting the individual from which the control body fluid sample is obtained to one which is healthy or one which has the atherosclerosis risk factor. These added limitations, which describe a step of comparing a profile of a tested individual to a control profile characteristic of a healthy individual or preferably one having a specific clinical condition so as to enable diagnosis of a clinical condition in the tested individual, clearly distinguish the claimed invention from Kasdan. Applicant wishes to emphasize that the teachings of Kasdan provide guidelines for preparation and analysis of a blood sample for the sole purpose of

counting blood cells. As is well known in the art, cell counting does not require use of controls, nor does it require treatment of samples under controlled flow conditions. Samples prepared for cell counts merely require that "*the particles of interest do not overlap each other*" in order to ensure accurate counts and as such, use of controls which are prepared under flow conditions similar to that of the tested sample is not required. Thus, the teachings of Kasdan only enable characterization of a sample as being either normal or abnormal. In sharp contrast, the instant teachings, as clarified by the instant amendments and new claims, enable diagnosis of a clinical condition, such as an inflammatory response, by comparison of a sample profile from a tested individual to a control sample profile. Furthermore, in sharp contrast to Kasdan, the instant teachings enable analysis of a very broad range of parameters, such as those related to substrate adhesion by particulate components, and thereby enable characterization of a sample according to any one of a broad range of specific clinical conditions, such an inflammatory response. Specification support for the newly added limitations is provided, for example, at page 40, sentence starting at line 19; page 43, paragraph starting at line 9; page 51, line 16 to page 52, line 6; and page 53, lines 7-12.

Applicant yet further currently elects to add new Claims 65 and 68, respectively depending from independent claims 37 and 48, including the limitation of the profile of particulate components in the body fluid sample being determined according to said differential distribution of said particulate components along at least one axis selected from the group consisting of an axis along a length of said substrate, an axis along a width of said substrate and an axis perpendicular to said substrate. This clearly distinguishes the claimed invention over the teachings of Kasdan since the latter teaches imaging of particles along a single plane corresponding to that of a horizontal device, such as a standard slide or flow-cell. Specification support for the language and limitation of new Claims 65 and 68 is provided, for example, at Claim 14, as originally filed and in the specification at page 9, lines 17-22.

In view of the above arguments and amendments, Applicant believes to have overcome the 35 U.S.C. § 103(a) rejections.

35 U.S.C. § 102(b) Rejections - U.S. Patent No. 5,822,447 to Kasdan

The Examiner has rejected claims 54-58 under 35 U.S.C. § 102(b) as being

anticipated by U.S. Patent No. 5,822,447 to Kasdan. The Examiner's rejections are respectfully traversed. Claims 54, 59 and 60 have now been amended. New Claims 71 and 72 have now been added.

With respect to Claim 54, the Examiner contends that Kasdan discloses a method of generating a profile of a body fluid sample comprising the steps of: (a) causing controlled flow of the body fluid sample on a substrate (column 1, line 62 to column 2, line 14), said controlled flow of the body fluid sample leading to a distribution of the body fluid sample on said substrate (column 2, lines 15-34); and (b) determining a thickness variance of the body fluid sample along a direction of said controlled flow on said substrate (column 2, lines 30-34).

With respect to Claim 55, the Examiner contends that Kasdan discloses the step of analyzing, and optionally characterizing, particulate components of said body fluid sample in at least one specific region of said substrate (column 2, lines 13-15).

With respect to Claim 56, the Examiner contends that Kasdan discloses that the step of analyzing and optionally characterizing particulate components in said body fluid sample is effected according to at least one parameter selected from the group consisting of estimated hemoglobin concentration, approximated leukocyte count and differential, approximated platelet count, degree of leukocyte aggregation, aggregate composition, degree of leukocyte, erythrocyte and/or platelet adherence towards the surface of said substrate, degree of red cell aggregation, degree of platelet aggregation, degree of leukocyte to erythrocyte interaction, degree of erythrocyte to platelet interaction and degree of leukocyte to platelet interaction (column 2, lines 1-5).

Applicant states that Claims 57-58 are analyzed and rejected similarly as above.

With respect to the Examiner's rejections of Claim 54, Applicant is in vigorous disagreement with the Examiner's contentions that Kasdan teaches a method comprising a step in accordance with the instant claims which: (i) leads to a distribution of a body fluid sample on a substrate, according to column 2, lines 15-34 of Kasdan; and/or (ii) includes determining a thickness variance of a fluid, according to column 2, lines 30-34 of Kasdan.

With respect to the Examiner's contention that Kasdan teaches a method comprising a step according to the instant claims leading to a distribution of a body

fluid sample on a substrate, Applicant wishes to respectfully point out that the body fluid sample according to Kasdan clearly does not correspond to the body fluid sample of the instant claims, for the following critical reasons. Namely, distribution of a body fluid sample on a substrate according to Kasdan consists of: (i) a constantly moving fluid (column 2, sentence starting at line 31) passing through a flow cell (column 2, sentence starting at line 15); (ii) in which the body fluid sample is surrounded by a sheath fluid (sentence starting at line 19), such that at no time does any component of the fluid sample actually adhere to a solid support; and (iii) in which the particulate components, are suspended in a moving fluid in a flow cell of expanding width (Kasdan, Figure 2, extended area 18a) such that these never form a fixed relative configuration with respect to each other. In sharp and critical contrast, however, distribution of a body fluid sample on a substrate according to the instant claims critically refers to particulate components (i.e. the instantly claimed "body fluid sample"; specification, page 23, sentence starting at line 4) of the fluid sample which adhere (i.e., the instantly claimed "body sample fluid sample on a substrate"; specification, page 23, sentence starting at line 4) to a solid support (i.e., the instantly claimed "substrate"; specification, page 22, sentence starting at line 10) so as to form a fixed configuration with respect to each other on the solid support (the instantly claimed "distribution of a body fluid sample on a substrate"; inherent feature of adherent particles on a solid support; specification, page 59 line 11 to page 62, line 9; and Figures 20-22 and legends thereof at page 20). As such, on this basis alone, Applicant is of the very strong opinion that Kasdan very clearly does not teach a method comprising a step which leads to a distribution of a body fluid sample on a substrate according to the instant claims, and thereby very clearly does not constitute anticipatory prior art to the instant claims, in sharp contrast to the Examiner's contention that it does.

With respect to the Examiner's contention that Kasdan teaches a method comprising a step which includes determining a thickness variance of a fluid in accordance with the instant claims, Applicant wishes to firstly respectfully point out that at no point do the cited passages of Kasdan, which refer to the flow-cell embodiment of this reference, either explicitly or implicitly, refer to determining a thickness variance of a fluid. Critically, as described above, Kasdan explicitly states as a general guideline for all embodiments of the invention taught therein: "*So long as*

the particles of interest do not overlap each other, the method of the present invention may be practiced." (Kasdan, column 2, sentence starting at line 6). Further critically, Kasdan explicitly states as a specific guideline relating to the flow-cell embodiment referred to by the Examiner: "*The sample fluid is distributed such that the particles of interest substantially do not overlap one another in the extended area... with the microscope focused on the extended area.*" (Kasdan, column 2, lines 25-29). Applicant wishes to emphasize that, in very sharp contrast to all possible configurations relating to the cited passages of Kasdan, the thickness variance taught by the instant claims refers to the thickness of the overlapping of particulate components of the body fluid sample on the substrate (specification, page 59, line 15 to page 60, line 1; page 60 line 21 to page 62 line 1; Figures 18-20). Hence, since Kasdan teaches that the particulate components of the body fluid sample must never overlap, it is, in Applicant's very strong opinion, inherently impossible for Kasdan to teach determining a thickness variance of a fluid in accordance with the instant claims. Applicant wishes to respectfully further point out that the "different portions" of the sample fluid referred to in the relevant passage cited by the Examiner clearly do not correspond, as apparently misinterpreted by the Examiner, to portions at different distances extending perpendicularly from the surface of the substrate (i.e. "thickness variance" according to the instant claims), but rather in sharp and critical contrast correspond to different portions within the plane of extended area 18a of the flow cell as shown in Figure 2 of Kasdan). As such, on this basis alone as well, Applicant is of the very strong opinion that Kasdan very clearly does not teach a method comprising a step which involves determining a thickness variance of a fluid in accordance with the instant claims, and thereby does not constitute anticipatory prior art, in sharp contrast to the Examiner's contention that it does.

With respect to the Examiner's rejections of Claims 55-58, Applicant respectfully traverses these rejections, and wishes to respectfully point out that Claims 55-58, which depend directly or indirectly from Claim 54, are not anticipated by Kasdan, by virtue of Claim 54 not being anticipated by Kasdan, in accordance with the argumentation set forth hereinabove.

Specifically with respect to the Examiner's rejections of Claim 56, namely that Kasdan at column 2, lines 1-5, discloses the parameters listed this claim Applicant wishes to firstly respectfully point out that the passages cited by the Examiner simply

refer to the fact that red and white blood cells may or may not be overlapping in a typical microscope smear, and do not refer to any of the parameters cited, nor to analysis thereof, nor to platelets. Indeed, Applicant wishes to point out that the cited passages very clearly teach away from analyzing and characteristic the parameters cited, in particular all parameters relating to inter-particle aggregation, inter-particle interaction and/or substrate adhesion. Namely, as described above, and as specifically and relevantly recited in the passages cited by the Examiner (column 2, lines 1-5, as well as in the immediately following lines 6-8), Kasdan specifically teaches that only sparsely distributed, non-overlapping cells can be used in the context cited by the Examiner. Since intercellular aggregation and/or intercellular interaction are essentially impossible to analyze in sparsely distributed, non-overlapping cells, Applicant is of the very strong opinion that the passages cited by the Examiner in fact very clearly teach away from practicing Claim 56. Furthermore, Applicant wishes to point out that Kasdan, in particular the passages thereof cited by the Examiner, provides no means whatsoever enabling analysis of a parameter relating to particle adherence to a substrate such as the "*degree of leukocyte, erythrocyte and/or platelet adherence towards the surface of said substrate*" taught by Claim 56 since such a parameter essentially cannot be analyzed by imaging of a "*typical microscopic smear*", which is the context of the Examiner's citation (column 1, line 67). As such, in Applicant's very strong opinion, Kasdan in fact very clearly teaches away from practicing all such aspects of Claim 56 relating to substrate adherence. In very sharp contrast, analysis of adherence of particulate components to a substrate according to Claim 56 is indeed very clearly taught and enabled by the instant teachings (specification, for example, page 23, sentence starting at line 4; page 57, Example 7, "Carrier Adhesion").

As such, Applicant is of the very strong opinion that Claims 55-58 are clearly not anticipated by Kasdan, in sharp contrast to the Examiner's contentions.

The above notwithstanding, Applicant currently elects to amend Claim 54 to now include the further step of comparing the profile of step (b) with a profile of a control body fluid sample obtained under the controlled flow, and new Claims 72 and 73 respectively limiting the control body fluid sample to one being derived from an individual which is healthy or which has a clinical condition. The relevance of such amendments for distinguishing the instant claims over the teachings of Kasdan, and

specification support for such amendments is amply described above under 35 U.S.C. § 103(a) Rejections (Kasdan).

In view of the above arguments and amendments, Applicant believes to have overcome the 35 U.S.C. § 102(b) rejections.

35 U.S.C. § 103(a) Rejections - U.S. Patent No. 5,822,447 to Kasdan in view of Patent No. 6,687,395 to Dietz et al.

The Examiner has rejected Claims 39-44 and 59-62 under 35 U.S.C. § 103(a) as being unpatentable over Kasdan in view of U.S. Patent No. 6,687,395 to Dietz *et al.* The Examiner's rejections are respectfully traversed. Claims 39 and 41 have now been cancelled rendering moot the Examiner's rejections of these claims. Claims 37, 38, 40, 42-45, 54, and 59-60 have now been amended. New Claims 65-67 and 71-72 have now been added.

The Examiner concedes that Kasdan is silent about a clinical condition caused by an agent selected from the group consisting of an infective agent and a chemical agent. Nevertheless the Examiner has rejected Claims 39 and 59-62 based upon the contention that these are rendered non-obvious in view of the Examiner's contentions that Kasdan discloses the method of Claim 56, and that Dietz *et al.* discloses a system for micro volume laser scanning cytometry comprising a clinical condition selected from the group consisting of an infective agent and a chemical agent. The Examiner concludes on the basis of such contentions that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to provide the clinical condition is caused by an agent selected from the group consisting of an infective agent and a chemical agent as thought by Dietz *et al.* with the apparatus and method of Kasdan in order to improve the accuracy of measuring cell type population changes and soluble factor changes during disease progression and during therapy.

As to Claim 60, the Examiner contends that Dietz *et al.*, at column 6, lines 4-25, discloses a clinical condition caused by a disorder selected from the group consisting of atherosclerosis, diabetes, viral infection and bacterial infection.

The Examiner further states that Claims 40-44 are similarly analyzed and rejected.

With respect to the Examiner's rejections of Claims 39-44, Applicant respectfully traverses the Examiner's rejections, and wishes to respectfully point out

that Claims 39-44, which depend directly or indirectly from Claim 37, are not rendered obvious by Kasdan in view of Dietz *et al.*, by virtue of Claim 37 not being rendered obvious by Kasdan, in accordance with argumentation set forth above under 35 U.S.C. § 103(a) Rejections (Kasdan), and by virtue of Claim 56 not being disclosed by Kasdan, in accordance with argumentation set forth above under 35 U.S.C. § 102(b) Rejections (Kasdan).

With respect to the Examiner's rejections of Claims 59-62, based upon Examiner's contention that Kasdan discloses Claim 56, Applicant respectfully traverses the Examiner's rejections, and wishes to respectfully point out that Claims 59-62, which depend directly or indirectly from Claims 54 and/or 56, are not rendered obvious by Kasdan in view of Dietz *et al.*, since as argued above, it is Applicant's strong opinion that the invention of Claims 54 and 56 is not described or suggested by Kasdan.

The above notwithstanding, Applicant currently elects, as described above, to: amend Claim 37, from which Claims 39-44 depend; amend Claim 54, from which Claims 59-61 depend; and add New Claims 65-67 and 71-72. The relevance of such amendments for clarifying the distinction between the instant claims over the teachings of Kasdan, and specification support for such amendments is amply described above under 35 U.S.C. § 103(a) Rejections (Kasdan) and 35 U.S.C. § 102(b) Rejections.

In view of the above arguments and amendments, Applicant believes to have overcome the 35 U.S.C. § 103(a) rejections (Kasdan in view of Dietz *et al.*).

In view of the amendments and remarks set forth above it is respectfully submitted that Claims 37-38, 40, and 42-72 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

Sol Sheinbein
Registration No. 25,457

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